

Etiology of febrile illnesses associated with seizures in children from LMICs: results from the FIEBRE study

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on behalf of the **FIEBRE collaborative group**

Background



- 1) Seizures associated with fever are common in children
 - **Banal infections** (febrile seizures)
 - **Life-threatening diseases** (meningitis or cerebral malaria)
- 2) LICs account for the **highest burden of neurological disease** (especially for neurotropic infections), while having far fewer resources than HICs
- 3) Seizures are present in more than the **10% of child admissions** in some sub-Saharan settings

1. WHO. The global burden of disease: 2004 update. Geneva: World Health Organization. 2008.
2. Yansouni CP, Bottieau E, Lutumba P, Winkler AS, Lynen L, Büscher P, et al. Rapid diagnostic tests for neurological infections in central Africa. The Lancet Infectious Diseases. 2013;13(6):546-58.
3. WHO W. Atlas: country resources for neurological disorders 2004. http://www.who.int/mental_health/neurology/neurogy_atlas..pdf (2004) (accessed August, 29th 2022).
4. Tebeila ND, Dangor Z, Madhi SA, Cutland C, Groome MJ. Incidence of febrile seizures and associated factors in children in Soweto, South Africa. S Afr Med J. 2021 Aug 2;111(8):796-802. doi: 10.7196/SAMJ.2021.v111i8.15431. PMID: 35227362.

Background



Southern Mozambique

Manhiça Morbidity Surveillance System

20 years: >1.2M visits and > 70K admissions



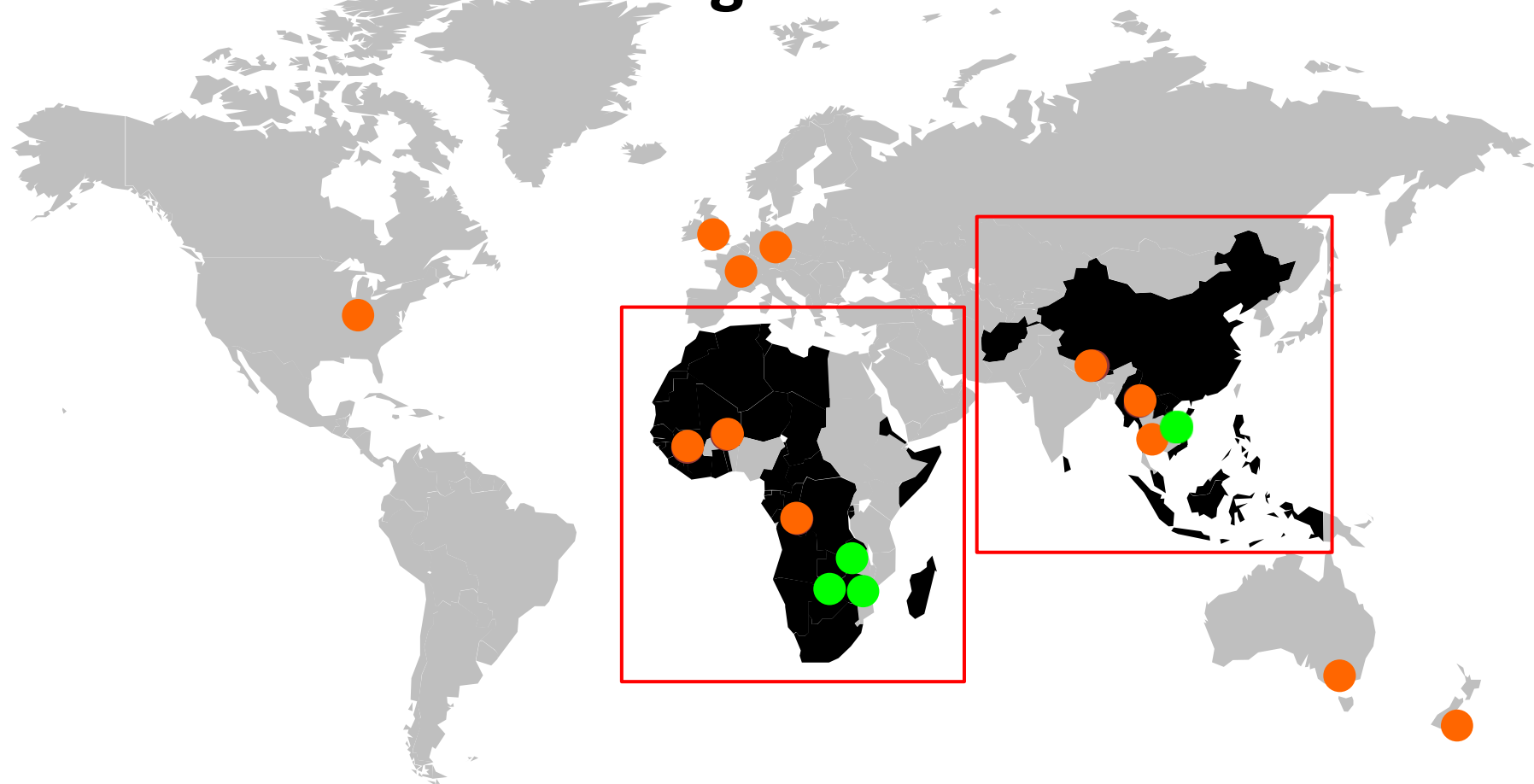
Seizures present in 0.55% visits (94% fever)

Seizures present in 13% of admissions.

Increased risk of **being admitted**
(OR 5.65, CI 5.19-6.15)

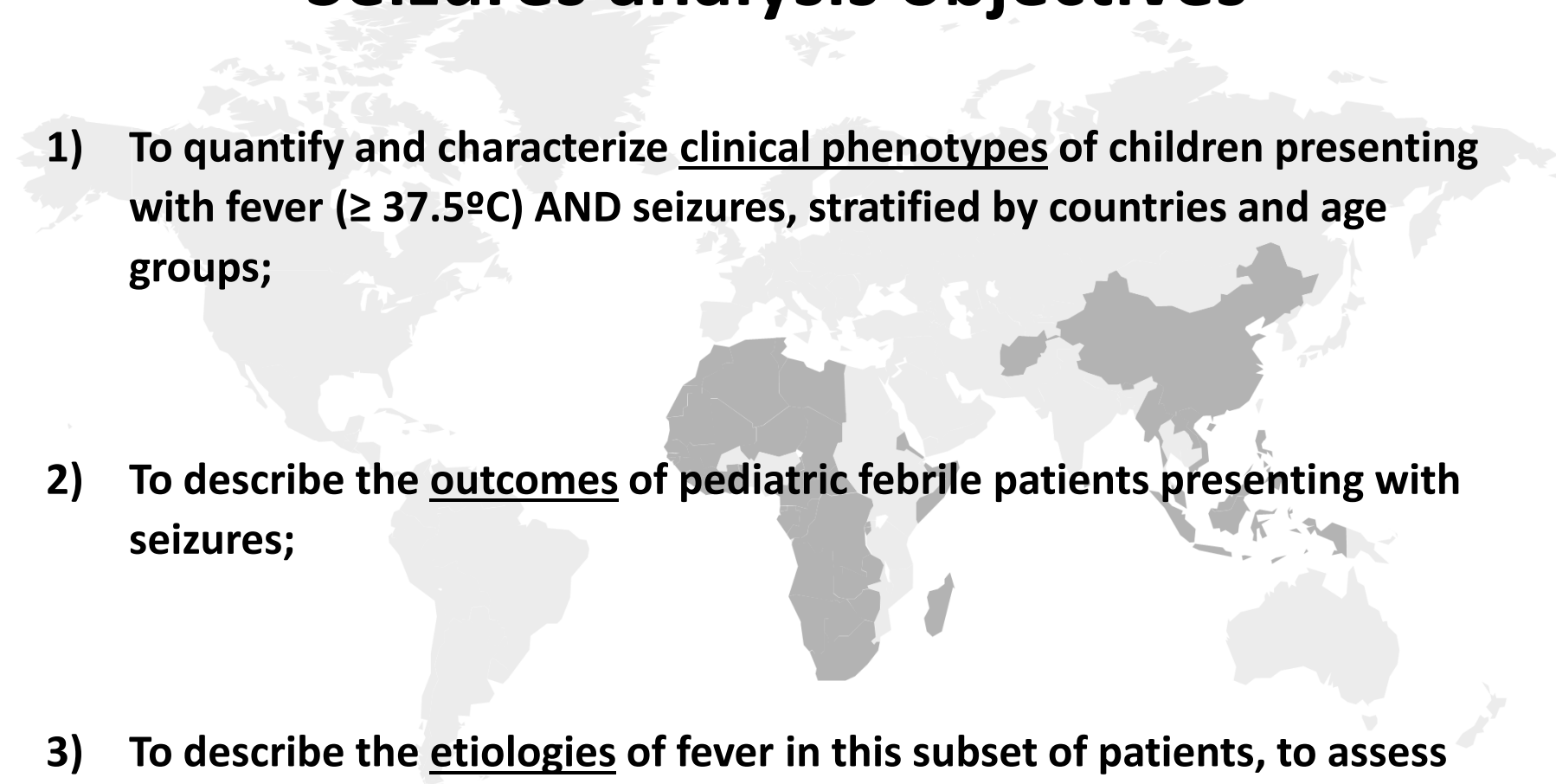
Increased risk of **death within 48h**
(OR 3.48, CI 2.22-5.4)

FIEBRE study, 2018-2023: Febrile Illness Evaluation in a Broad Range of Endemicities



- Study site
- Reference laboratory

Seizures analysis objectives

- 
- 1) To quantify and characterize clinical phenotypes of children presenting with fever ($\geq 37.5^{\circ}\text{C}$) AND seizures, stratified by countries and age groups;
 - 2) To describe the outcomes of pediatric febrile patients presenting with seizures;
 - 3) To describe the etiologies of fever in this subset of patients, to assess future interventions.

Methods

1) Standardized clinical evaluation

1) Initial clinical suspicion (list of diagnoses, yes/no answers, non-exclusive)

2) Seizures definition:

- **Reported** by caregivers (within the febrile episode) and / or **observed**.
- The **number of days** since the onset of seizures was also recorded.

2) Samples: Venous **blood**, **pharyngeal** swabs, +/- **urine** sample

3) On-site laboratory tests:

- **Malaria** (HRP2-pLDH combo rapid diagnostic test, microscopy)
- **Blood culture** & susceptibility
- **HIV**
- **Urine dipstick + culture**

4) Follow-up on day +28 after recruitment. Outcome: **alive** (better / worse/ same) / **dead** / **LFU**

5) 1:2 **healthy community controls** recruited to calculate attributable fractions of fever for each pathogen

Reference laboratory testing for centralized, standard diagnosis according to clinical case definitions

INFECTION	REFERENCE LAB FOR TESTING OR QC
Bacterial/fungal <u>bloodstream or urinary tract infection</u>	MALDI-TOF & confirmation of susceptibility
Bloodstream <u>Mycobacteria</u> infection	Subculture, line probe assay or sequencing, & susceptibility testing
<u>Arboviral</u> infection: chikungunya, dengue, Japanese encephalitis, o'nyong nyong, Zika	ELISA, plaque reduction & neutralization test
<u>Rickettsial</u> infection: Q fever (Coxiella burnetii), scrub typhus, spotted fever group rickettsioses, typhus group rickettsioses	Immunofluorescence antibody test & nucleic acid amplification test
<u>Brucellosis</u>	Microagglutination test (MAT)
<u>Leptospirosis</u>	Microagglutination test (MAT)
<u>Leishmaniasis</u>	Direct agglutination test (DAT)
<u>Histoplasmosis</u>	Serum Histoplasma antigen detection
<u>Respiratory</u> infections: influenza, RSV, other	Luminex nucleic acid amplification test
<u>Malaria</u> and other (<u>Borrelia spp</u>)	Microscopy of blood smear

Results

Total children recruited

3749

Seizures in 391

11%

Lao PDR

760

12.5%

346

Outpt

12.7%

414

Inpt

12.3%

Malawi

952

14.2%

603

Outpt

0.3%

349

Inpt

32.4%

Mozambique

1161

11%

615

Outpt

0.6%

548

Inpt

22.4%

Zimbabwe

876

6.2%

521

Outpt

1.5%

355

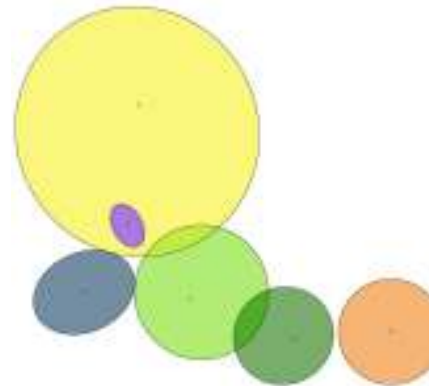
Inpt

13%

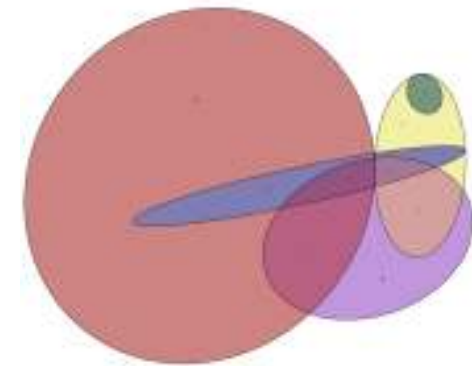
Clinical suspicion

Children with seizures (n=391)		
Clinical suspicion	n (%)	χ^2 p-value
Malaria	155 (39.6)	<0.001
Fever of unknown origin	120 (30.7)	<0.001
URTI	31 (7.9)	<0.001
Sepsis	30 (7.7)	0.61
LRTI	28 (7.2)	0.17
GI	28 (7.1)	0.17
CNS infection	24 (6.1)	<0.001
UTI	0 (0)	/

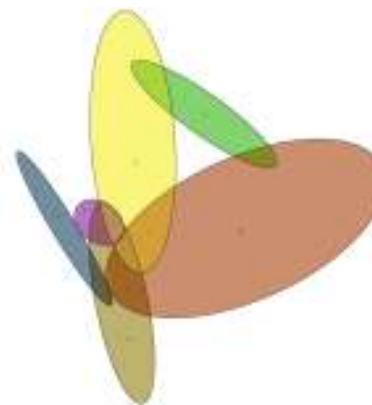
Lao PDR



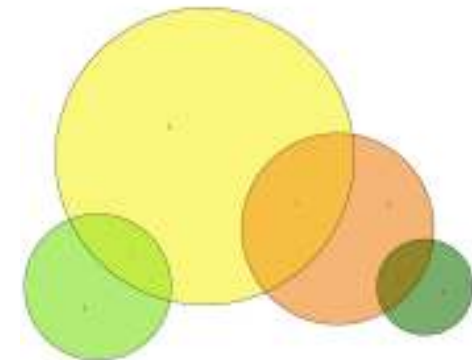
Malawi



Mozambique

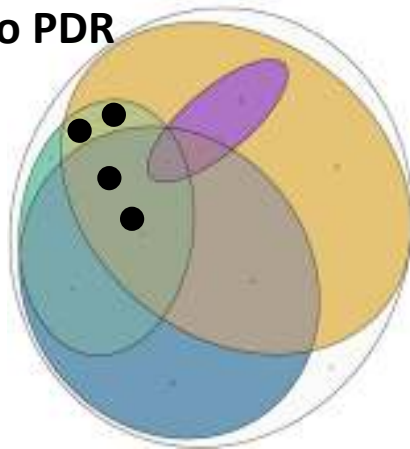


Zimbabwe

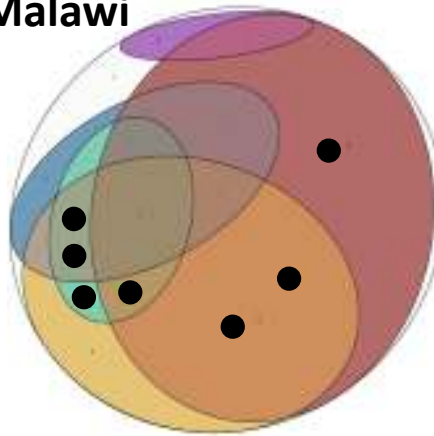


Clinical phenotypes and fatal outcomes

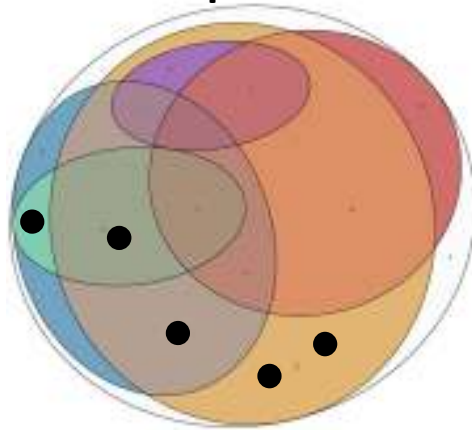
Lao PDR



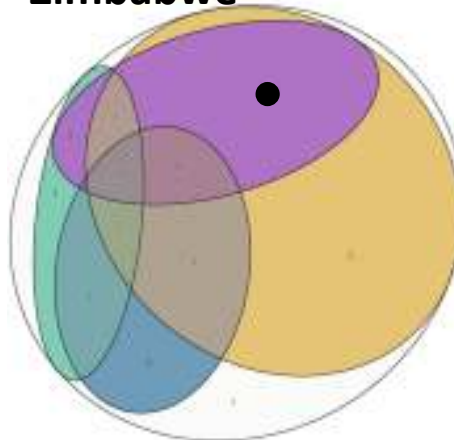
Malawi



Mozambique



Zimbabwe



● Deaths (n=17)

Children with seizures (n=391)

Clinical phenotypes	n (%)
potential CNS infection	389 (99)
potentially severe infection (danger signs)	249 (64)
URTI	151 (42.1)
Malaria	147 (39.4)
LRTI	79 (20.3)
Abdominal infection	50 (18.8)

Outpatients

Outpatients with seizures	All sites	Lao PDR	Malawi	Mozambique	Zimbabwe
	n (%)	n (%)	n (%)	n (%)	n (%)
	58 (2.7)	44 (12.7)	2 (0.3)	4 (0.6)	8 (1.5)
Age					
Median	4 [IQR 3.8 - 10]	6 [IQR 3.8 - 11]	2.5	2.5	4
<1 year	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1-5 years old	22 (2.3)	14 (12.3)	1 (0.3)	2 (0.6)	5 (2.1)
6-15 years old	36 (3.5)	30 (13.1)	1 (0.4)	2 (0.7)	3 (1.1)
Test results					
+ blood culture	Preliminary - Incomplete reference laboratories results - Attributable fractions (community controls)				
+ urine culture					
+ malaria test					
+ NPS*					
+ brucella					
+ leptospirosis					
Outcome day 28					
alive	44 (100)	32 (100)	2 (100)	4 (100)	6 (100)
dead	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LFU	43 (12.9)	3 (5.9)	12 (10.6)	20 (16.3)	8 (17.4)

Inpatients

Inpatients with seizures	All sites n (%)	Lao PDR n (%)	Malawi n (%)	Mozambique n (%)	Zimbabwe n (%)
	333 (20)	51 (12.3)	113 (32.4)	123 (22.4)	46 (13)
Age					
Median	3.2 [IQR 2- 6]	5 [IQR 1.2 - 8]	3.4 [IQR 2- 6]	3 [IQR 2 - 6]	2 [IQR 1.1 - 2.5]
<1 year	17 (9.9)	7 (14.9)	4 (12.9)	5 (7.9)	1 (3.2)
1-5 years old	193 (24.2)	17 (9.4)	68 (41.2)	78 (29.7)	30 (16.0)
6-15 years old	123 (17.6)	27 (14.5)	41 (26.8)	40 (18)	15 (10.9)
Test results					
+ blood culture	Preliminary - Incomplete reference laboratories results - Attributable fractions (community controls)				
+ urine culture					
+ malaria test					
+ NPS*					
+ brucella					
+ leptospirosis					
Outcome day 28					
alive	273 (94.1)	44 (91.7)	94 (93.1)	98 (95.1)	37 (97.4)
dead	17 (5.9)	4 (8.3)	7 (6.9)	5 (4.9)	1 (2.6)
LFU	43 (12.9)	3 (5.9)	12 (10.6)	20 (16.3)	8 (17.4)

Inpatients

Inpatients with seizures	All sites n (%)	Lao PDR n (%)	Malawi n (%)	Mozambique n (%)	Zimbabwe n (%)
Age					46 (13)
Median					IQR 1.1 - 2.5]
<1 year					1 (3.2)
1-5 years old					30 (16.0)
6-15 years old					15 (10.9)
Test results					
+ blood culture					0 (0)
+ urine culture					0 (0)
+ malaria test					0 (0)
+ NPS*					22 (47.8)
+ brucella	1 (0.3)	0 (0)	1 (0.9)	0 (0)	0 (0)
+ leptospirosis	1 (0.3)	1 (2.0)	0 (0)	0 (0)	0 (0)
Outcome day 28					
alive	273 (94.1)	44 (91.7)	94 (93.1)	98 (95.1)	37 (97.4)
dead	17 (5.9)	4 (8.3)	7 (6.9)	5 (4.9)	1 (2.6)
LFU	43 (12.9)	3 (5.9)	12 (10.6)	20 (16.3)	8 (17.4)

Mortality

With seizures: **5.9%**

Without seizures: **0.86%**

OR 6.17, CI 3.29-11.56

Conclusions



- 1) Seizures are a very common presentation among febrile children in our settings
- 2) Seizures are associated with a high risk of mortality
- 3) *Preliminary results:* malaria and respiratory tract pathogens are common among children with fever and seizures.

Conclusions



- 4) Clinical phenotypes are overlapping among children with seizures, and are not sufficient for an appropriate decision-making**
- 5) We need tools to appropriately identify benign febrile seizures (avoid unnecessary admissions) and high-risk patients (reduce mortality)**
- 6) Our final etiology results will help us characterize better both groups**
- 7) Host-targeted biomarkers could have a potential role in the decision-making process**



*Maita basa, zikomo,
korp jai (ຂອບໃຈ), kanimambo, obrigada,
thanks for your interest and attention!*

Comments, questions?

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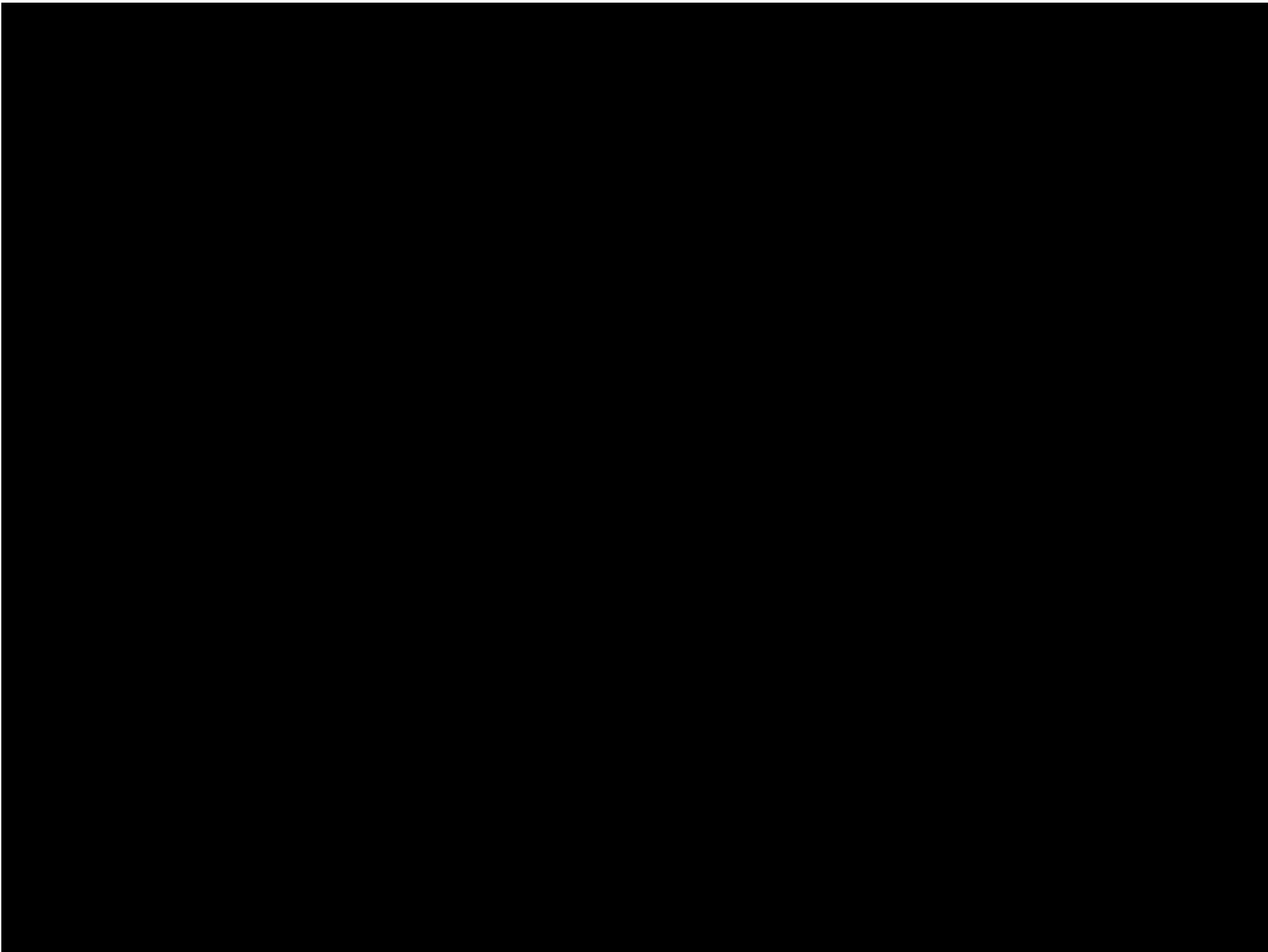
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Mortality

Patient	Demographics		Comorbidities		Laboratory results	
	Country	Age group	HIV +	Wasting	Positive malaria	Positive NPS
1	Laos	1-5y				
2		<1y				
3		5-15y				
4		5-15y				
5	Malawi	1-5y				
6		5-15y				
7		5-15y				
8		5-15y				
9		1-5y				
10		5-15y				
11	Mozambique	1-5y				
12		1-5y				
13		<1y				
14		1-5y				
15	Zimbabwe	1-5y				
16		1-5y				
17		5-15y				



parainfluenza 2



rhinovirus

Outpatients

Febrile child patients presenting with seizures - OUTPATIENTS	All sites	Lao PDR	Malawi	Mozambique	Zimbabwe
	n (%)	n (%)	n (%)	n (%)	n (%)
Children with seizures	58 (2.7)	44 (12.7)	2 (0.3)	4 (0.6)	8 (1.5)
Age					
Median 4 [IQR 3.8 - 10]	6 [IQR 3.8 - 10]				
<1 year	0 (0)				
1-5 years old	22 (2.3)				
6-15 years old	36 (3.5)				
Test results					
positive blood culture	6 (10.3)				
positive urine culture	0 (0)				
positive malaria test	3 (0.05)				
positive NPS*	29 (50)				
positive brucella	0 (0)				
leptospirosis	1 (1.7)				
Outcome day 28					
alive	44 (100)	32 (100)	2 (100)	4 (100)	6 (100)
dead	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LFU	43 (12.9)	3 (5.9)	12 (10.6)	20 (16.3)	8 (17.4)

Pathogens

Staphylococcus species - not *S. aureus*

Staphylococcus species - not *S. aureus*

Staphylococcus species - not *S. aureus*

Acinetobacter baumannii

Escherichia coli

Salmonella typhi

Inpatients

Febrile child patients presenting with seizures – OUTPATIENTS	All sites n (%)	Lao PDR n (%)	Malawi n (%)	Mozambique n (%)	Zimbabwe n (%)
Children with seizures	58 (2.7)	44 (12.7)	2 (0.3)	4 (0.6)	8 (1.5)
Age					
Median	4 [IQR 3.8 - 10]	6 [IQR 3.8 - 10]			
<1 year	0 (0)				
1-5 years old	22 (2.3)	1 (0.3)			
6-15 years old	36 (3.5)	3 (0.9)			
Test results	9 (2.7)				
positive blood culture	6 (10.3)				
positive urine culture	0 (0)				
positive malaria test	3 (0.05)				
positive NPS*	29 (50)	2 (5.9)			
positive brucella	0 (0)				
leptospirosis	1 (1.7)				
Outcome day 28					
alive	44 (100)	3 (5.9)	12 (10.6)	20 (16.3)	8 (17.4)
dead	0 (0)				
LFU	43 (12.9)				

Pathogens

Staphylococcus aureus

Staphylococcus species - not Staph. aureus

Staphylococcus species - not Staph. aureus

Escherichia coli

Streptococcus pneumoniae

Klebsiella (Enterobacter) aerogenes

Micrococcus species

Staphylococcus aureus

Staphylococcus aureus

Outpatients

Febrile child patients presenting with seizures - OUTPATIENTS	All sites	Lao PDR	Malawi	Mozambique	Zimbabwe
	n (%)	n (%)	n (%)	n (%)	n (%)
Children with seizures	58 (2.7)	14 (12.7)	2 (0.3)	4 (0.6)	8 (1.5)
Age					
Median	4 [IQR 3.8 - 10]	6 [IQR 3-10]	3 [IQR 2-9]	4 [IQR 3-10]	4 [IQR 3-10]
<1 year	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1-5 years old	22 (2.3)	10 (9.1)	2 (0.3)	2 (0.3)	2 (0.4)
6-15 years old	36 (3.5)	4 (3.6)	0 (0)	2 (0.3)	6 (1.1)
Test results					
positive blood culture	6 (10.3)	0 (0)	0 (0)	0 (0)	0 (0)
positive urine culture	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
positive malaria test	3 (0.05)	0 (0)	0 (0)	0 (0)	0 (0)
positive NPS*	29 (50)	10 (71.4)	2 (100)	4 (100)	8 (100)
positive brucella	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
leptospirosis	1 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)
Outcome day 28					
alive	44 (100)	10 (71.4)	2 (100)	4 (100)	8 (100)
dead	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LFU	43 (12.9)	3 (5.9)	12 (10.6)	20 (16.3)	8 (17.4)
NPS positive results					
Influenza B					13
Rhinovirus					6
Respiratory Syncytial Virus - A					3
Human bocavirus					3
Adenovirus					2
Enterovirus					2
Parainfluenza 1					2
Influenza A H1					1
Parainfluenza 3					1
Coronavirus NL63					1
Coronavirus OC43					1
Number of pathogens /patient					1 [IQR 1-2]

Inpatients

Febrile child patients presenting with seizures - INPATIENTS	All sites	Lao PDR	Malawi	Mozambique	Zimbabwe
n (%)	NPS positive results	N			
Children with seizures	333 (20)	Rhinovirus	22		
Age		Enterovirus	15		
Median	3.2 [IQR 2- 6]	Adenovirus	12		
<1 year	17 (9.9)	Human bocavirus	6		
1-5 years old	193 (24.2)	Respiratory Syncytial Virus - A	5		
6-15 years old	123 (17.6)	Parainfluenza 3	5		
Test results		Influenza A H1	4		
positive blood culture	9 (2.7)	Influenza A H3	3		
positive urine culture	0 (0)	Influenza B	3		
positive malaria test	144 (43.2)	Parainfluenza 1	3		
positive NPS*	65 (19.5)	Metapneumovirus	3		
positive brucella	1 (0.3)	Parainfluenza 4	2		
leptospirosis	1 (0.3)	Coronavirus OC43	2		
Outcome day 28		Clamidophila pneumoniae	2		
alive	273 (94.1)	Parainfluenza 2	1		
dead	17 (5.9)	Number of pathogens /patient	2 [IQR 1-3]		
LFU	43 (12.9)				

Clinical phenotypes

Clinical phenotype	Variables
CNS syndrome/ Meningoencephalitis	convulsions during this illness OR lethargic/decreased alertness OR BCS<5 OR convulsing on presentation OR stiff neck OR bulging fontanelle OR prostration*
Severe illness (≥2 IMCI general danger signs or ED-PEWS ≥30)	(2+ general IMCI danger signs OR (1 general IMCI danger sign AND (WFH< -3 z score OR WFA <-3 z scores OR muac<11.5))) OR ED-PEWS ≥30
Ear/upper respiratory tract infection	(cough OR ear pain OR stridor OR ear exudate OR red/bulging tympanic membrane OR tender ear swelling OR tonsillar exudate OR runny nose)
Malaria	Malaria positive RDT
Lower respiratory tract infection	At least 2 of cough OR difficulty breathing OR fast breathing OR chest indrawing OR grunting OR O2 Sats ≤92% OR wheeze OR abnormal chest sounds on auscultation
Abdominal or pelvic infection	pain on passing urine OR positive urine dip OR abdominal pain OR abdominal tenderness

Children with seizures (n=391)	
Clinical phenotypes	n (%)
CNS infection	389 (100)
Severe infection	249 (64)
URTI	151 (42.1)
Malaria	147 (39.4)
LRTI	79 (20.3)
Abdominal infection	50 (18.8)

Febrile child patients presenting with seizures	total	<1 year	1-5 years	6-15 years
Total	391 (10.4%)	17 (6.3)	215 (12.2)	159 (9.3)
Comorbidities				
positive HIV status	15 (3.8)	0 (0)	4 (1.9)	11 (6.9)
Malnutrition	51 (13.2)	5 (29.4)	37 (17.2)	9 (5.7)
Clinicians suspicion				
CNS infection	24 (6.1)	0 (0)	11 (5.1)	13 (8.2)
Malaria	155 (39.6)	4 (23.5)	95 (44.2)	56 (35.2)
URTI	31 (7.9)	3 (17.6)	17 (7.9)	11 (6.9)
LRTI	28 (7.2)	1 (5.9)	19 (8.8)	8 (5)
GI	28 (7.1)	3 (17.6)	14 (6.5)	9 (5.7)
UTI	0 (0)	0 (0)	0 (0)	0 (0)
Soft tissue infection	9 (2.3)	1 (5.9)	4 (1.9)	4 (2.5)
Osteomuscular infection	0 (0)	0 (0)	0 (0)	0 (0)
Sepsis	30 (7.7)	2 (11.8)	21 (9.8)	7 (4.4)
Fever of unknown origin	120 (30.7)	5 (29.4)	56 (26.0)	59 (37.1)
Clinical phenotypes				
CNS infection	389 (99.5)	17 (100)	214 (99.5)	158 (99.4)
URTI	151 (42.1)	7 (41.2)	88 (40.9)	56 (35.2)
LRTI	79 (20.3)	3 (17.6)	34 (15.8)	42 (26.4)
Malaria	147 (39.4)	2 (11.8)	96 (44.7)	49 (30.8)
Severe infection	249 (64)	14 (82.4)	133 (61.9)	102 (64.2)
Abdominal infection	50 (18.8)	0 (0)	27 (12.6)	23 (14.5)
Bone / soft tissue infection	2 (0.5%)	0 (0)	0 (0)	2 (1.3)
Test results				
positive blood culture	15 (4.0)	1 (5.9)	7 (3.3)	7 (4.4)
positive urine culture	0 (0)	0 (0)	0 (0)	0 (0)
positive malaria test	155 (39.6)	4 (23.5)	95 (44.2)	56 (35.2)
positive NPS*	94 (24)	4 (23.5)	59 (27.4)	31 (19.5)
positive brucella	1 (0.6)	0 (0)	0 (0)	1 (0.6)
leptospirosis	2 (0.7)	0 (0)	0 (0)	2 (1.3)
Outcome day 28				
alive	317 (81.1)	14 (82.4)	175 (81.4)	128 (80.5)
dead	17 (4.3)	2 (11.8)	8 (3.7)	7 (4.4)
LFU	56 (14.6)	1 (5.9)	32 (14.9)	24 (15.1)